

## PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB1747f-PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/50377	International filing date (day/month/year) 13.08.2003	Priority date (day/month/year) 15.08.2002
International Patent Classification (IPC) or both national classification and IPC C07D498/12		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
  
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
  - This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.
  
3. This report contains indications relating to the following items:
  - I  Basis of the opinion
  - II  Priority
  - III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV  Lack of unity of invention
  - V  Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI  Certain documents cited
  - VII  Certain defects in the international application
  - VIII  Certain observations on the international application

Date of submission of the demand  24.01.2004	Date of completion of this report  25.11.2004
Name and mailing address of the International preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Steendijk, M Telephone No. +49 89 2399-8460
	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP 03/50377

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-44 as originally filed

**Claims, Numbers**

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50377

- 1) The present application relates to fused heterocyclic isoxazoline derivatives having alpha2-adrenoceptor antagonistic and serotonin reuptake inhibitory activity and their application in medicaments for the treatment of i.a. depression.
- 2) The following documents are cited:  
D1: EP-A-0 361 577  
D2: WO 99 67237 A  
D3: EP-A-0 885 883  
D4: WO 95 07893 A  
D5: WO 97 25317 A  
D6: WO 02 066484 A

Document D6 was published after the filing date of the present application. As this priority seems validly claimed, document D6 is herein not considered as prior art.

- 3) Novelty  
Document D1 relates to tetrahydronaphthalene and indane derivatives having alpha2-adrenoceptor antagonistic and serotonin reuptake inhibitory activity, not however fused isoxazoline derivatives.  
Document D2 relates to 5-HT1a antagonistic benzoxazoles.  
Documents D3-D5 relate to dopamine receptor ligands; the particular structure of the presently claimed compounds is not disclosed.

It is noted that document D6 describes compounds with alpha2-adrenoceptor antagonistic and serotonin reuptake inhibitory activity of a closely related structure; the specific groups for Het as presently defined are however not mentioned in D6

Novelty may therefore be acknowledged.

- 4) Inventive step  
The application defines a solution to the problem of providing further agents with alpha2-adrenoceptor antagonistic and serotonin reuptake inhibitory activity.  
Considering the relevant activity, document D1 may be considered as closest prior art. The compounds of the present application show such major structural difference with the compounds of D1, that the person skilled in the art could not have expected the activity of the present compounds as a matter of obviousness.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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**5) Further observations**

It is noted that the present claim 1 refers to optional substitutions for Het and R3. It is not evident what substitutions are intended . It is further noted that in as far as any (optional) substitution is intended, the claims are likely to cover compounds which will not exhibit the relevant activity and will thus not present a solution to the relevant problem.

It is not evident what additional compounds will be covered by the definition of claim 5 which are not already covered by the broadly formulated claim 1.